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Antibiotics as an Intracanal Medicament in Endodontics

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Abstract

Bacteria have been implicated in the pathogenesis and progression of pulp and periapical diseases. The primary aim of endodontic treatment is to remove as many bacteria as possible from the root canal system and then to create an environment in which any remaining organisms cannot survive. This can only be achieved through the use of a combination of aseptic treatment techniques, chemomechanical preparation of the root canal, antimicrobial irrigating solutions and intracanal medicaments. The choice of which intracanal medicament to use is dependent on having an accurate diagnosis of the condition being treated, as well as a thorough knowledge of the type of organisms likely to be involved and their mechanisms of growth and survival. Since the disease is likely to have been caused by the presence of bacteria within the root canal, the use of an antimicrobial agent is essential. Many medicaments have been used in an attempt to achieve the above aims but no single preparation has been found to be completely predictable or effective[1].

Keyword*: Antibiotics, Antimicrobial efficacy, Intracanal medicament.*

INTRODUCTION

Microorganisms have been well known to play a role in pulpal and periapical diseases. The bacteria associated with primary endodontic infections are mixed, but are predominantly gram-negative anaerobic rods, whereas the bacteria associated with secondary infection comprise only one or a few bacterial species – most important of which is *Enterococcus facecalis*[2].Eradication of causative microorganisms during root canal treatment procedures helps attain successful results.

Because of the complex nature of the root canal system and the presence of many inaccessible areas, a combination of mechanical instrumentation and irrigation is necessary to decrease the amount of bacteria/micro-organisms in the root canal system. [3]However chemo- mechanical preparation is often not enough, and many bacteria may remain in the root canal system.[4-6]

Intracanal medicaments in endodontics have been used for a number of reasons including the elimination or reduction of microorganisms, rendering canal contents inert, prevention of post-treatment pain, and to enhance anesthesia. Calcium hydroxide is the most commonly used intracanal medicament, however its efficacy towards *Enterococcus facecalis* is questionable[7]. Waltimo et al. found that calcium hydroxide dressing between appointments did not show the expected effect in disinfecting the root canal system and in treatment outcome. [8]

In the recent years, a new concept has been developed, which employs the use of a combination of anti bacterial drugs (metronidazole, ciprofloxacin and minocycline) for disinfection of pulpal and periradicular lesions. It has been reported that this mixture can sterilize root dentin. [3]

MEDICAMENTS

Medicaments are used as an aid to improve the predictability and prognosis of endodontic treatment. They are used in endodontic therapy in order[9-11] to:

- eliminate or destroy any remaining viable bacteria in the root canal system that have not been destroyed by the chemomechanical preparation processes (i.e., instrumentation and irrigation),
- reduce periradicular inflammation and hence reduce pain,
- help eliminate apical exudate if it is present,
- prevent or arrest inflammatory root resorption if it is present, and
- prevent re-infection of the root canal system by acting as both a chemical and a physical barrier if the temporary or interim restoration breaks down.

Inter-appointment intracanal medication has been unequivocally shown to contribute to favourable out-comes when treating endodontic infections[14-18].The need for intracanal medication is greater in those cases where bacteria are resistant to routine treatment, and where the therapy cannot be successfully completed due to the presence of pain or continuing exudate[19]. Some endodontic conditions are ideally treated over several appointments which may be extended over a long period of time. This allows various medicaments to be used depending on the status of the pulp, the periapical tissues, the hard dental tissues (such as cementum) and the condition of the apical foramen (i.e., “open”, or fully developed and unaffected by resorption)[3]. The minimum inter-appointment time interval should be no less than 14 days, since inflammation takes at least 10–14 days to subside or heal,[20] but longer periods are generally more desirable as most medicaments take 3–4 weeks to reach their maximum concentration within the peripheral dentine[21]. In addition, if signs or symptoms are not subsiding, then a longer period of medication time or an alternative medicament may be necessary. Many hand and rotary instrumentation techniques tend to produce round preparations (especially in oval canals) leaving some areas uninstrumented and hence possibly containing infected debris. It has been estimated that as much as 50 per cent of

the canal wall may remain uninstrumented during preparation. The remaining necrotic tissue remnants may provide a source of nutrition for any surviving bacteria[22,23]. In addition, bacteria are likely to remain in dentinal tubules after instrumentation. If this occurs, calcium hydroxide and other disinfectants that require direct physical contact with pathogens may be ineffective[24]. The longstanding popular notion of entombment and perishing of intraradicular microbes following treatment lacks scientific validity[24,25]. The presence of micro- organisms inside a root canal may not necessarily lead to the failure of treatment, but their absence will certainly favour healing[26].

ANTIBIOTICS

Commercial preparations in this group contain either one or a combination of antibiotics, and sometimes incorporate other compounds such as corticosteroids. Antibiotics can be used as an adjunct to endodontic treatment in a number of ways – locally (i.e., intracanal), systemically and prophylactically[27].

The focus for this review will be the local use of antibiotics in the form of intracanal medicaments. As discussed above, bacteria may be present within areas of the root canal system that are inaccessible to irrigants and to the mechanical cleaning processes within the canal. Hence, an antibiotic contained within an intracanal medicament must be able to diffuse into these areas to reduce the number of viable bacteria. If such a reduction is achieved, an improved periapical healing response would be expected[27]. The first reported local use of an antibiotic in endodontic treatment was in 1951 when Grossman used a polyantibiotic paste known as PBSC[28]. PBSC contained penicillin to target Gram-positive organisms, bacitracin for penicillin-resistant strains, streptomycin for Gram-negative organisms, and caprylate sodium to target yeasts – these compounds were all suspended in a silicone vehicle.

Although clinical evaluation suggested that the paste conferred a therapeutic effect, the composition was ineffective against anaerobic species which are now appreciated as being the dominant organisms responsible for endodontic diseases. In 1975, the USA Food and Drug Administration banned PBSC for endodontic use primarily because of the risks of sensitization and allergic reactions attributed to penicillin[29]. The two most common antibiotic-containing commercial paste preparations currently available are Ledermix™ paste (Lederle Pharmaceuticals, Wolfsratshausen, Germany) and Septomixine Forte™ paste (Septodont, Saint-Maur, France). Both of these preparations also contain corticosteroids as antiinflammatory agents. Septomixine Forte contains two antibiotics – neomycin and polymixin B sulphate. Neither of these can be considered as suitable for use against the commonly reported endodontic bacteria because of their inappropriate spectra of activity[27]. Nystatin replaces sodium caprylate as an antifungal agent and is available in the form of PBSN. Due to potential for sensitivity in topical use in allergic patient PBSN has largely fallen in usage.

Neomycin is bactericidal against Gram-negative bacilli but it is ineffective against Bacteroides and related species, as well as against fungi. Polymyxin B sulphate is ineffective against Gram-positive bacteria, as shown by Tang *et al*[30]. who demonstrated that a routine one-week application of Septomixine Forte was not effective in inhibiting residual intracanal bacterial growth between appointments.

In addition, although the anti inflammatory (corticosteroid) agent, dexamethasone (at a concentration of 0.05%), is clinically effective, triamcinolone is considered to have less systemic side effects[27]. In 1948, the first synthetic tetracycline, chlortetracycline, was developed and marketed by Lederle Pharmaceuticals. Subsequently, this company developed the drug demethylchlortetracycline HCl (also known as demeclocycline HCl) which became the antibiotic component of Ledermix paste. Ledermix paste was developed by Schroeder and Triadan in 1960, and was released for sale in Europe by LederlePharmaceuticals in 1962. The primary interest of Schroeder and Triadan in the development of Ledermix paste was based on the use of corticosteroids to control pain and inflammation while the antimicrobial properties at the time were catered for by a formalin based paste called Asphalin (introduced in 1921). The sole reason for adding the antibiotic component to Ledermix paste was to compensate for what was perceived to be a possible corticoid-induced reduction in the host immune response. Schroeder and Triadan initially incorporated chloramphenicol in their first trials but when Lederle Pharmaceuticals became the manufacturer, the antibiotic was changed to demeclocycline HCl[31].

Today, Ledermix paste remains a combination of the same tetracycline antibiotic, demeclocycline HCl (at a concentration of 3.2%), and a corticosteroid, triamcinolone acetonide (concentration 1%), in a polyethylene glycol base. The two therapeutic components of Ledermix paste(i.e., triamcinolone and demeclocycline) are capable of diffusing through dentinal tubules and cementum to reach the periodontal and periapical tissues[3]. Abbott *et al*. showed that the dentinal tubules were the major supply route of the active components to the periradicular tissues, while the apical foramen was not as significant as a supply route. The concentration of demeclocycline within Ledermix paste itself (i.e., as it would be when placed within the root canal) is high enough to be effective against susceptible species of bacteria. However, within the peripheral parts of the dentine and in the periradicular tissues, the concentration achieved through diffusion is insufficient to inactivate bacteria, especially over time. Immediately adjacent to the root canal wall, inhibitory levels of demeclocycline are achieved for all reported bacteria within the first day of application but this level drops to about onetenth of the initial level after one week in both the midroot and apical third levels.

Further away from the root canal towards the cementum, the concentration of demeclocycline after one day is not high enough to inhibit growth of 12 of the 13 strains of commonly reported endodontic bacteria[27].Tetracyclines are bacteriostatic rather than bactericidal, and it is well known that yeasts are resistant to tetracyclines[3,32]. Tetracyclines exhibit a level of substantivity due to their

ability to form complexes with bivalent and trivalent cations. It is for this same reason that they are deposited in teeth and bones during calcification[33]. Abbott *et al*.[34] demonstrated that tetracyclines form a strong reversible bond with hard tissues and that they exhibit slow release over an extended period of time. The combination of antibiotics with a corticosteroid paste, as in Ledermix paste, has been used to arrest external inflammatory root resorption, and this effect has been documented histologically in an *in vivo* study[35]. Since it does not have damaging effects upon the periodontal ligament tissues, Ledermix is an effective medication for the treatment of inflammatory root resorption in traumatized teeth[3]. The immediate or early use of Ca(OH)2 following replantation has been shown to exacerbate replacement resorption due to its high pH and toxicity, and should therefore be discontinued[35,36]. Ledermix is now the preferred medicament to use immediately after replantation as it reduces both inflammatory and replacement resorption.

While not all authorities would agree with this view, the beneficial effects in terms of reducing resorption have been demonstrated in dogs by Bryson *et al*[36]. In teeth with 60 minutes of dry extra-alveolar time, immediate placement of Ledermix paste resulted in 59 per cent of the root surface showing favourable healing compared with only 14 per cent when calcium hydroxide was used immediately following replantation. Ledermix paste also resulted in greater preservation of root mass, hence maintaining function of the replanted teeth for longer[36]. The combination of Ledermix paste with calcium hydroxide was advocated by Schroeder, initially for the treatment of necrotic teeth with incomplete root formation.66 A 50:50 mixture of Ledermix paste and calcium hydroxide has also been advocated as an intracanal dressing in cases of infected root canals, pulp necrosis and infection with incomplete root formation (as an initial dressing prior to using calcium hydroxide alone for apexification), perforations, inflammatory root resorption, inflammatory periapical bone resorption and for the treatment of large periapical radiolucent lesions[3]. It has been shown that the 50:50 mixture results in slower release and diffusion of the active components of Ledermix paste which makes the medicament last longer in the canal[37].

This in turn helps to maintain the sterility of the canal for longer and also maintains a higher concentration of all components[37] within the canal. The 50:50 mixture of Ledermix paste and calcium hydroxide pastes does not alter the pH to any noticeable extent[38] and therefore it is expected that the mixture will act in a similar manner to when calcium hydroxide is used alone. Taylor *et al*.[38] also showed that for two indicator micro-organisms, *Lactobacillus casei* and *Streptococcus mutans* (which are cariogens), the 50:50 mixture was marginally more effective than either paste used alone. However, Seow[39] showed that for *Streptococcus sanguis* and *Staphylococcus aureus*, the addition of only 25 per cent by volume of Calyxl (a calcium hydroxide in saline paste) (Otto and Co., Frankfurt, Germany) to Ledermix converted the zone. of complete inhibition originally seen in Ledermix to one of only partial inhibition.

This latter study suggested that some medicaments should not be used in combination, and that when two medicaments with strong antimicrobial activity are combined there may be no additive or synergistic effects. Due to the complexity of root canal infections, it is unlikely that any single antibiotic could result in effective and predictable disinfection of all canals. More likely, a combination would be needed to address the diverse flora encountered. A combination of antibiotics would also decrease the likelihood of the development of resistant bacterial strains. Hoshino et al.[40] determined that a combination of ciprofloxacin, metronidazole and minocycline, each at a concentration of 25μg per ml (0.0025 per cent) of paste, was able to disinfect infected root dentine in vitro. Sato et al.76 found that this combination at 50μg of each antibiotic per mL (0.005 per cent) was sufficient to disinfect infected root dentine in situ. However, it is questionable whether this concentration would be adequate in vivo, particularly in immature teeth which present many challenges for their disinfection, including the potential for periapically-derived fluid to have a washing-out effect on the antibiotic paste via the open apical foramen. As already discussed, Portenier et al.[41] demonstrated that dentine itself can have an inhibitory effect on the bactericidal activity of intracanal medicaments.

Therefore, Windley et al.[42] used metronidazole, ciprofloxacin and minocycline in a thick paste at a concentration of 20mg of each drug per mL (i.e., 2 per cent) to counteract these potential effects. Of the 30 samples from which bacteria were cultured before treatment, 90 per cent remained positive following irrigation with 10mL of sodium hypochlorite, but this dropped to 30 per cent following the application of the triple antibiotic paste for two weeks[42]. In a study by Chu et al.,[43] Ledermix paste, Septomixine Forte, and Calasept (a calcium hydroxide in saline paste) (Nordiska Dental, Angleholm, Sweden) were spiraled into root canals and left for seven days. Bacteriological samples were taken before and after the two-visit endodontic treatment. The mean number of colony forming units (CFU) was reduced to 0.39 per cent after seven days, and the percentages of canals that remained with positive growth were 48 per cent, 31 per cent and 31 per cent respectively for each medicament. There were no significant differences in the number of canals with positive growth or mean CFU after instrumentation, irrigation and medication with Ledermix, Septomixine Forte or Calasept.

It was postulated that the results may be due to the synergistic balance between strict anaerobes, facultative anaerobes and other aerobes in endodontic infections being disrupted by antibiotics not specifically targeting the predominant flora. The incidence of postoperative pain following endodontic treatment varies from 16 to 48.5 per cent, and this symptom can last for several hours up to several days. The effectiveness of corticosteroid preparations in decreasing periapical inflammation secondary to chemomechanical instrumentation of the root canals was demonstrated by Smith et al.[44] who also showed histologically that fibroblastic and osteoblastic

activity was not eradicated by the use of 2.5% hydrocortisone. Ledermix paste has also been shown to be useful in reducing the incidence of pain following chemomechanical preparation of root canals[32,45].

Dentine acts as a slow release mechanism for triamcinolone to the periodontal tissues which is the probable basis of its long-acting therapeutic effect[33]. Ehrmann et al.[45] have shown that Ledermix paste provides greater postoperative pain relief compared to teeth medicated with calcium hydroxide, and this has been confirmed by several other studies[32,44,46,47,48]. As an example, Negm[48] reported that more than 85 per cent of cases had complete relief of pain after a one hour interval and more than 93 per cent were free of pain within 24 hours of treatment.

Root canal infections are polymicrobial, consisting of both aerobic and anaerobic bacteria. Because of the complexity of the root canal infection, it is unlikely that any single antibiotic could result in effective sterilization of the canal. A combination would be needed to address the diverse flora encountered. The most commonly used medicament is a combination of three antibiotics, referred to as a triple antibiotic paste (TAP). This formulation was first used by Sato et al. and contains metronidazole, ciprofloxacin, and minocycline. This combination is commercially available as 3-MIX MP [49].

Metronidazole is a nitroimidazole compound. It isselectively toxic to anaerobic microbes. It also exhibits broad spectrum antimicrobial activity against against protozoa and anaerobic bacteria. The presence of certain redox proteins reduces the nitro group of this compoundand generates free radicals that enter the cell and induce DNA damage. This results in rapid cell death [50].

Tetracyclines, which includes doxycycline and minocycline are primarily bacteriostatic, inhibiting protein synthesis by binding to 30S ribosomes in susceptible organisms. They exhibit broad spectrum of activity against gram positive and gram negative microorganisms. Minocycline is a semisynthetic derivative of tetracycline with a similar spectrum of antibacterial activity. Tetracycline inhibits collagenases and matrix metalloproteinases,and is not cytotoxic. It also increases the level of interleukin-10, an anti-inflammatory cytokine [51,52]. Ciprofloxacin is a synthetic floroquinolone with rapid bactericidal action. It inhibits the enzyme bacterial DNA gyrase, which nicks the double stranded DNA, introduces negative supercoil and then reseals the nicked end. The bactericidal action probably results from digestion of DNA by exonucleases whose production is signalled by the damaged DNA. It exhibits very potent activity against gram negative bacteria but very limited activity against gram positive bacteria. Most of the anaerobic bacteria are resistant to ciprofloxacin. Hence it is often combined with metronidazole in treating mixed infections.

CONCLUSION

Elimination of microbial contamination from the root canal system is a prerequisite to the successful outcome of root canal treatment. The evidence shows that mechanical instrumentation, irrigation, and use of inter appointment medication were all important in this regard. However, all of the currently available antimicrobial materials for root canal irrigation and medication have limitations, and the search continues for the ideal irrigant and intra-appointment medicament.

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